Enhanced phasic GABA inhibition during the repair phase of stroke: a novel therapeutic target.

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Public Summary:
Ischemic stroke is a leading cause of severe long-term disability that lacks drug therapies able to improve function during the repair phase of stroke, which occurs in the days to months after stroke onset and involves repair of surviving neurons and growth of new ones. Figuring out the mechanisms that promote this neuronal plasticity is critical for the development of new therapeutics with a broad treatment window. Inhibiting baseline, or tonic, GABA signaling during the repair phase was reported to enhance functional recovery in mice, suggesting that GABA plays an important role in brain repair. While baseline GABA appears to suppress brain repair after stroke, less is known about the role of active, or phasic, GABA during the repair phase. We observed an increase in phasic GABA signaling in mice within the area around the infarct area. Furthermore, we demonstrate that enhancing phasic GABA signaling using zolpidem, a Food and Drug Administration (FDA)-approved GABA-positive modulator, during the repair phase improved stroke recovery. These data identify enhancing phasic GABA signaling as a novel therapeutic strategy, indicate zolpidem's potential to improve recovery, and underscore the necessity to distinguish the role of tonic versus phasic GABA signaling in stroke recovery.

Scientific Abstract:
Ischaemic stroke is the leading cause of severe long-term disability yet lacks drug therapies that promote the repair phase of recovery. This repair phase of stroke occurs days to months after stroke onset and involves brain remapping and plasticity within the peri-infarct zone. Elucidating mechanisms that promote this plasticity is critical for the development of new therapeutics with a broad treatment window. Inhibiting tonic (extrasynaptic) GABA signalling during the repair phase was reported to enhance functional recovery in mice suggesting that GABA plays an important function in modulating brain repair. While tonic GABA appears to suppress brain repair after stroke, less is known about the role of phasic (synaptic) GABA during the repair phase. We observed an increase in postsynaptic phasic GABA signalling in mice within the peri-infarct cortex specific to layer 5; we found increased numbers of alpha1 receptor subunit-containing GABAergic synapses detected using array tomography, and an associated increased efficacy of spontaneous and miniature inhibitory postsynaptic currents in pyramidal neurons. Furthermore, we demonstrate that enhancing phasic GABA signalling using zolpidem, a Food and Drug Administration (FDA)-approved GABA-positive allosteric modulator, during the repair phase improved behavioural recovery. These data identify potentiation of phasic GABA signalling as a novel therapeutic strategy, indicate zolpidem's potential to improve recovery, and underscore the necessity to distinguish the role of tonic and phasic GABA signalling in stroke recovery.